Does Effect of a Neuroprotective Agent on Volume of Experimental Animal Cerebral Infarct Predict Effect of the Agent on Clinical Outcome in Human Stroke?[a]

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INTRODUCTION

A major experimental approach to the study of neuroprotection against stroke is the performance of a putatively neuroprotective maneuver in a laboratory animal who has a focal cerebral ischemic lesion created by an arterial occlusion procedure. Typically, results are judged from comparison of infarct volume in treated versus control animals. Human stroke treatment trials in which the endpoint is typically degree of recovery of function—rather than infarct volume—have been carried out using agents tested in such animal studies.

To base human clinical outcome trials on these laboratory studies requires the assumption that infarct volume reductions in animals predict clinical benefit in humans. We herein report the preliminary findings of our attempt to test this assumption through correlation of available human results with the results of animal studies using the same treatment. We reviewed the available literature through August 31, 1996. We found reports of randomized clinical trials of five treatments for acute stroke for which there are suitable animal data. One of these five treatments (the thrombolytic agent tissue plasminogen activator, tPA) has been approved by the United States Food and Drug Administration (FDA) for use in stroke; the other four treatments (glucocorticoids, ganglioside GM_1 (GM_1), hemodilution, nimodipine) have not been so approved. We summarize the animal and then the clinical data below and follow with our interpretations.

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EXPERIMENTAL ANIMAL RESULTS

TABLE 1 gives the treatment, the time at which the treatment was begun relative to zero time (the time of induction of arterial occlusion in the laboratory animal), and the relative size of infarct with active versus control treatment.

FIGURE 1 shows regression lines assembled from all the data in TABLE 1 for each of five treatments. All minus times (prophylactic treatment) have been converted to −5 minutes for ease of display. The glucocorticoid line and the hemodilution line each combine values from several agents as reported in several different papers; the same is true for thrombolysis (tPA, urokinase). For ease of display the figure shows only the first 60 minutes of the thrombolysis line, although the regression line of which this is a segment incorporates the 120–360-minute values.

It will be noted that the regression lines all slope up toward y = 1.0 (total failure: infarct size with treatment equals that without treatment). For glucocorticoid treatment the line intercepts y = 0 at zero time; for nimodipine, y = 0.93 at zero

TABLE 1. Times and Relative Infarct Size for Treatments with tPA, Urokinase, GM_1, Nimodipine, Hemodilution, and Glucocorticoid

Author	Treatment	Time (Mins)[a]	Rel. Infarct Size[b]
Sakurama[16]	tPA	5	0.18
	tPA	180	0.40
	tPA	360	0.56
	urokinase	5	0.28
Sereghy[17]	tPA	30	0.20
Carter[18]	tPA	60	0.50
Overgaard[19]	tPA	120	0.23
Del Zoppo[20]	urokinase	180	0.21
Simon[21]	GM_1	−5	0.56
	GM_1	5	0.56
	GM_1	15	0.78
	GM_1	30	0.79
Borzeix[22]	GM_1	60	1.12
Bielenberg[23]	nimodipine	−30	0.61
Marinov[24]	nimodipine	−20	0.60
Wassman[25]	nimodipine	−20	0.69
Barnett[26]	nimodipine	−15	0.84
Rickels[27]	nimodipine	−5	0.75
Sakaki[28]	nimodipine	−5	0.46
Snape[29]	nimodipine	5	1.20
Cole[30]	hemodilution	−90	0.37
Rickels	hemodilution	−5	0.55
Matsui[31]	hemodilution	30	0.97
Matsui	hemodilution	30	0.88
Koç[32]	hemodilution	60	0.42
Tuor[33]	glucocorticoid	−240	0.15
Kim[34]	glucocorticoid	0	1.05

[a] Time (Mins) = time of initiation of treatment with regard to zero time: the time of induction of carotid artery occlusion.

[b] Rel. Infarct Size = mean infarct size in treated animals divided by mean infarct size in control animals.

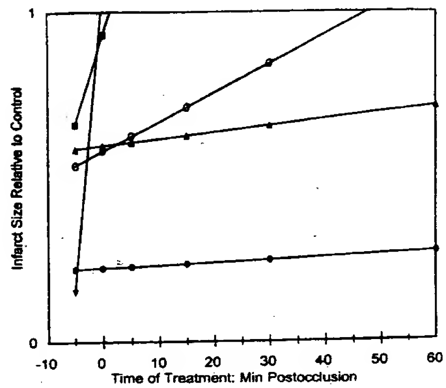

FIGURE 1. Regression lines for animal results with five treatments. The data are from TABLE 1. ● Thrombolytics (includes tPA and urokinase); ⊖ GM_1; ■ nimodipine; ▲ hemodilution; and ▼ glucocorticoid (includes methylprednisolone and dexamethasone).

time and reaches 1.0 by 2 minutes. For GM_1, y = 0.57 at zero time and 1.0 at 50 minutes. The hemodilution line—zero time value of 0.58—would reach y = 1.0 at 2.9 hours. By contrast, for tPA y = 0.23 at zero time, and the regression line projects to 0.36 at 3 hours and to 0.49 at 6 hours.

RESULTS OF CLINICAL TRIALS

Thrombolysis

In the National Institute of Neurological Disorders and Stroke/NIH (NINDS)[1] trial of tPA, 624 patients were entered within 3 hours of onset of ischemic stroke (48% within 1.5 hours); treatment with the thrombolytic agent was associated with a trend toward increased survival and with statistically significant improvement in function of survivors at 3 months.

Four other clinical trials in 1892 ischemic stroke patients failed to show benefit among patients receiving thrombolytic agents. These were the European Cooperative Acute Stroke Study (ECASS) six-hour window tPA trial,[2] the Multicentre Acute Stroke Trial–Italy (MAST-I) six-hour window streptokinase trial,[3] the Multicentre Acute Stroke Trial–European Study Group (MAST-E) six-hour window streptokinase trial,[4] and the Australian Streptokinase Trial Study Group (ASK) four-hour window (21% entered within 3 hours) streptokinase trial.[5]

All four failed trials showed a high incidence of parenchymatous hematomas: 13.3–26.9% with thrombolytic treatment versus 2.9–10.6% among the controls. These rates stand in contrast to those of the successful NINDS trial, where symptomatic or fatal intracranial bleeding was seen within the first 36 hours following treatment in only 3.8% of tPA patients and in 0.6% of the controls. It appears that the excess of cerebral hemorrhages in these four studies caused their failure.

With regard to this disparity in cerebral bleeding: in all four failed studies aspirin or anticoagulants were either required or permitted during the first 24 hours; only in the NINDS study were such treatments rigorously forbidden.

The FDA has approved rt-PA when it can be started within 3 hours of onset of ischemic stroke, with the use of anticoagulants or antiplatelet agents excluded during the next 24 hours.

GM_1

Two GM_1 studies totaling 1079 patients showed no benefit. These were the Early Stroke Trial (EST):[6] 792 patients, 5-hour window; and the Sygen Acute Stroke Study (SASS):[7] 287 patients, 48-hour window.

GM_1 has not been approved by the FDA for stroke treatment.

Hemodilution

Five studies involving 1012 ischemic stroke patients were done during the computerized tomography (CT) scanning era. Strand *et al.*[8] reported benefit in 102 patients (treatment begun within 48 hours of stroke). However, the Scandinavian Stroke Study Group trial[9] (373 patients, 8-hour window), Frei *et al.*[10] (62 patients, 30-hour window), Bayer *et al.*[11] (173 patients, 48-hour window), and Goslinga *et al.*[12] (300 patients, 48-hour window) all failed to find benefit. The Italian Acute Stroke Study Group[13] treated 1267 patients within 12 hours of stroke onset (702: <6 hours; 565: 6–12 hours); 87% of the strokes were infarcts and 13% were hemorrhages. There was no benefit, including after early treatment, for ischemic or for hemorrhagic stroke.

Hemodilution treatment for stroke is not an FDA-approved maneuver.

Glucocorticoid

Millikan *et al.*[14] give in their Table 8-4 their analysis of the results of glucocorticoid treatment for "progressing stroke and acute cerebral infarction" in eight trials from 1956 to 1978. In one study the window was 24 hours; the other seven studies had 48-hour windows. Millikan *et al.* judged that 38% of 244 treated patients and 37% of 216 controls had improved; deaths were 39% and 36%, respectively. Thus, no benefit was recognized.

Glucocorticoid treatment for stroke is not an FDA-approved maneuver.

Nimodipine

The results of nine trials of nimodipine in acute ischemic stroke were summarized by Kaste *et al.*[15] Three studies from 1988 to 1989 totaling 442 patients (entry within 12 hours in one study, within 24 hours in the other two) showed benefit; seven studies from 1990 to 1994 ($n = 3327$; entry within 48 hours) showed no benefit.

The FDA has not approved nimodipine for stroke treatment.

DISCUSSION

This discussion is based on the assumption that the combined wisdom of the drug sponsors and of the FDA (with regard to which treatments should be submitted to the FDA for judgement and which should be approved) is correct, and therefore that tPA treatment does have a beneficial effect in stroke while GM_1, hemodilution, glucocorticoids, and nimodipine do not. Could we have predicted these conclusions from the animal studies? Retrospective analysis suggests that we could have made accurate predictions by paying attention to the time windows during which a beneficial effect was seen in animals and to the strength of that benefit.

As noted above in the section on laboratory results, the animal study regression line for thrombolytic treatment shows considerable reduction of infarct volume for treatment initiated across the 0–3-hour window: y value of 0.23 at zero time and 0.36 at three hours. The NINDS stroke trial showed favorable functional outcomes across this same time window. The congruity between these results is compatible with the view that reduction in animal infarct size in a given time window predicts human functional outcome benefit for treatment begun within that window.

In contrast to thrombolytic therapy, the animal study regression lines for the failed treatments with GM_1, hemodilution, glucocorticoids, and nimodipine show much poorer zero time y values (0.57 or worse), and all reach total failure (y = 1.0) between zero minutes and 2.9 hours. Thus, from the animal work, there is no reason to infer that these treatments can produce a neuroprotective effect except when given very early. Therefore, the failure to see clinical benefit in stroke trials in which many patients entered long after closure of the windows for success in animals (in all but 1 of 27 clinical trials the entry windows were wider than 5 hours; 18 studies had 48-hour windows) could be viewed as predicted by the animal results.

CONCLUSIONS

The correlations between laboratory and clinical results for five putatively neuroprotective treatments are compatible with the view that the influence of such a treatment on infarct size in animals during a given time window predicts human functional outcome responses to this treatment in the same time window; to the extent that the time window of the human trial extends beyond the window of successful animal results, the beneficial outcomes of early human treatment can be predicted to be diluted to total failure in later-entering patients, to the disadvantage of the overall results.

Prospective analysis of other data sets is desirable.

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